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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,241	06/26/2000	NORIAKI HATTORI	193582US0PCT	3276

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/22/2003 15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,241	HATTORI ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-39,41,43,44 and 46-52* is/are rejected.

7)☒ Claim(s) *40,42 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 10, 2003 has been entered.

The amendment filed March 10, 2003 canceling claims 14-33 and adding claims 34-52 has been entered.

Claims 34-52 are pending.

Priority

Receipt is acknowledged of an English translation of foreign priority document JP 361022/1997 submitted under 35 U.S.C. 119(a)-(d).

Specification

The specification is objected to because of the following informalities: the name "Cleoptera" given on page 6, line 2, is different from "Coleoptera" recited in claim 34. The correct version of the word should be used in all instances.

The specification recites "North American firefly luciferase activity decreases to about 20% in the presence of 0.1% benzalkonium chloride (Table 1)" (page 2, lines 4-5). However, the data presented in Table 1 were obtained in the presence of 0.4% benzalkonium chloride (page 19).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-39, 41 and 43-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 34 recites 89.3% in the presence of 0.1% benzalkonium chloride. While the specification teaches the emission rate of 89.3% in the presence of 0.4%

benzalkonium chloride (page 19, Table 1, HIK), the examiner is unable to locate adequate support in the specification for 89.3% in the presence of 0.1% benzalkonium chloride.

Claims 38 and 50 recite "0.01% of the surfactant" and "0.01% cationic surfactant", respectively. While the specification has support for 0.01% of benzalkonium chloride (page 20), the Examiner is unable to locate adequate support in the specification for such limitations, i.e. for 0.01% of any surfactant. Furthermore, while the specification teaches the emission rate of 89.3% in the presence of 0.4% benzalkonium chloride (page 19, Table 1, HIK), the examiner is unable to locate adequate support in the specification for "89.3% in the presence of at least 0.01% of the surfactant" (claim 38, emphasis added). Thus, there is no indication that the above limitations were within the scope of the invention as conceived by Applicants at the time the application was filed.

Claim 35, with dependent claims 39, 41 and 43-52, recites "99.6% identical". The Examiner is unable to locate adequate support in the specification for such percent identity.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 34, 44 and 46-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 34 is directed to a mutant *Coleoptera* luciferase of any structure and properties having an improved luciferase activity that is 89.3% in the presence of 0.1% benzalkonium chloride compared to the luciferase activity in the absence of benzalkonium chloride. Claim 44 is drawn to a DNA encoding the mutant luciferase of claim 34. Claims 46-52 depend directly or ultimately from claim 34.

Order Coleoptera includes several Families of organisms having different physiological and biochemical properties. There is no limitations on the structure of mutant luciferase.

Thus, the claims are drawn to or depend from a large genus of mutant luciferases from *Coleoptera* having an improved luciferase activity that is 89.3% in the presence of 0.1% benzalkonium chloride. Therefore, said genus of mutants is characterized by function.

Applicants disclose two mutants of *Luciola lateralis* (HEIKE) luciferase having an improved activity that is at least 89.3% in the presence of 0.4% benzalkonium chloride having sequences of SEQ ID NOs: 4 and 6. Therefore, a representative number of a mutant luciferase is two. Moreover, the specification fails to describe any other

representative species from the genus of mutant *Coleoptera* luciferases by any identifying characteristics or properties other than the "functionality" of having an improved luciferase activity that is 89.3% in the presence of 0.1% benzalkonium chloride and fails to provide any structure: function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 34-39, 44 and 46-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutant *L.* luciferases having the sequences of SEQ ID NO:4 or SEQ ID NO:6, does not reasonably provide enablement for a mutant *Coleoptera* luciferase of any structure and properties having an improved luciferase activity that is 89.3% in the presence of 0.1% benzalkonium chloride and for a mutant luciferase having an amino acid sequence that is 99.6% identical to the wild type GENJI or HEIKE and having an improved luciferase activity that is 89.3% in the presence of any surfactant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 34 is directed to a mutant *Coleoptera* luciferase of any structure and properties having an improved luciferase activity that is 89.% in the presence of 0.1% benzalkonium chloride compared to the luciferase activity in the absence of benzalkonium chloride. Claim 35 is directed to a mutant luciferase having an amino acid sequence that is 99.6% identical to the wild type GENJI or HEIKE and having an improved luciferase activity that is 89.3% in the presence of any surfactant. Dependent claim 36 limits surfactant to cationic and dependent claim 38 limits the concentration of any surfactant to 0.01%. Dependent claim 39 requires mutation at position 490.

Claim 34 encompasses any mutant *Coleoptera* luciferase with unknown possible low homology to the luciferase of *L. lateralis* having the requisite property, *supra*. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant luciferase enzymes

and genes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of two mutant luciferases having one or two amino acids different compared with the wild-type sequence.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any mutant luciferase having the requisite property with an undisclosed homology to the luciferase of *L. lateralis* and any mutant luciferase with no or low

homology to the luciferase of *L. lateralis* in which the amino acid corresponding to residue 490 of *L. lateralis* luciferase is not necessarily mutated or is mutated (claim 39) or polynucleotides encoding therefor because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting luciferase activity; (B) the general tolerance of luciferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any luciferase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

In addition, with regard to claim 35 and claims dependent therefrom, the specification provides no direction as to how to make a mutant luciferase having a structure other than SEQ ID NO:4 or 6 having precisely 89.3% activity when a surfactant other than 0.4% benzalkonium chloride is used (page 19, Table 1). It is expected from the state of the art, that the minimal changes in the protein structure would result in at least minimal changes in its activity.

Therefore, the specification lacks in guidance as to how to maintain the same precise activity of 89.3% in the presence of benzalkonium chloride concentrations other than 0.4 % and as low as 0.01% or in the presence of any other surfactant.

Furthermore, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably

correlated with the scope of the claims broadly including any number of amino acid modifications of any mutant *Coleoptera* luciferase with no or low homology to the luciferase of *L. lateralis* having the desired property in which the amino acid corresponding to residue 490 is or is not mutated. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of luciferases and genes therefor having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-39, 41, 43, 44 and 46-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 is confusing because it is drawn to an isolated "mutagenized" polypeptide, said isolated polypeptide belongs to the Order *Coleoptera*. There is a contradiction between the claimed polypeptide being a mutant and at the same time belonging to a naturally occurring organism. Amending the claim to refer to a mutant polypeptide wherein a wild-type polypeptide derived from the Order *Coleoptera*, for

example, is suggested. Further, claim 34 recites "said improved luciferase activity" and "the luciferase activity". It is unclear whether the activities of a mutant are compared at different conditions or the activity of a mutant is compared to a luciferase in which a mutation has not been introduced.

Claim 35 refers to an amino acid sequence having 99.6% identity to an amino acid sequence that is not defined. It is impossible to calculate identity without knowing the exact base sequence.

Furthermore, dependent claim 39 is indefinite for its recitation of the amino acid position 490 without indicating a sequence identifier of the sequence were said position is located. Reference to a SEQ ID NO: of a wild-type luciferase would obviate this rejection.

Claims 34 and 35 refer to activity without indicating conditions under which it is measured. Conditions such as pH, temperature, time, etc., is known to effect the activity. Therefore, without indicating conditions, the activity is not defined.

Claims 41 and 43, dependent from claim 35, are confusing as referring to changes relative to mutant sequences of SEQ ID NO:4 and SEQ ID NO:6, respectively, while 99.6% identity is indicated relative to the wild type sequences.

Claims not specifically rejected herein are rejected as dependent from the rejected base claim.

Allowable Subject Matter

Claims 40, 42 and 45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

Response to Arguments

Applicant's arguments filed March 10, 2003 have been fully considered but they are not persuasive with regard to the statement that "the claims contain both structural and functional limitations" for the reasons explained above in the rejections (Remarks, page 6).

The 102(e) rejection over Hirokawa et al. (US Patent 6,074,859, SEQ ID NO:14) is withdrawn. The examiner agrees that Hirokawa et al. is not entitled to priority under 35 U.S.C.§ 119 (e) to Provisional Application Number 60/051,917 with regard to SEQ ID NO: 14 because SEQ ID NO:14 is not disclosed in said provisional application (Remarks, pages 6-7).

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE**

FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner